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Relationship between clinical improvement and functional gains with clozapine in schizophrenia

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Abstract
Impairment in psychosocial functioning is a key feature in schizophrenia, but few studies have examined the relationship between improvements in symptoms and functioning. We examined the relationship between change in symptoms and change in functioning in a group of patients with treatment-resistant schizophrenia after 6 and 12 weeks of clozapine treatment. Participants were assessed prior to clozapine and again at 6 and 12-week on the 18-item Brief Psychiatric Rating Scale (BPRS) and the Social and Occupational Functioning Scale (SOFAS). Change scores in BPRS and SOFAS at 6 and 12-week post-clozapine were calculated and the direct relationship was assessed via regression models. Forty-three participants were included in this study; age of sample was 42.1±12.7 years, with 31 (72.1%) male participants. At baseline, the mean BPRS total and SOFAS scores were 46.98±12.86 and 33.07±10.79, respectively. There were significant improvements in BPRS total and SOFAS scores at 6 weeks, but no significant differences between 6 and 12-week assessments. There was no significant change in negative symptoms at both follow-up assessments. At 6-week, change in symptoms was not correlated with change in functioning and while the relationship between change in symptoms and functioning was stronger at 12 weeks, none of the BPRS factors emerged as a significant predictor. The present study found that lower baseline SOFAS score was the most robust predictor for improvements in SOFAS at 6 and 12-weeks. There appears to be a "ceiling"

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for functional improvements on clozapine, but follow-up studies are needed to examine functional gains beyond 12 weeks.

1. Introduction

Schizophrenia represents one of the leading causes of disability globally (Whiteford et al., 2013), with its core features (i.e. positive symptoms, negative symptoms and cognitive impairment) each contributing toward the observed psychosocial impairment, and hence the resultant disability (van Os and Kapur, 2009). Negative symptoms and cognitive impairment have both been shown to independently predict current and longer term functional outcomes, though evidence on the relative importance of either on functioning remains conflicting (Ayesa-Arriola et al., 2013; Fervaha et al., 2014b, 2014c; Foussias et al., 2011; Foussias and Remington, 2010; Mohamed et al., 2008; Perlick et al., 2008). Reasons for this have been attributed to sample differences (i.e. between first-episode, chronic and community-dwelling schizophrenia) and timing of assessments (Breier et al., 1991; Goldman et al., 1993; Johnstone et al., 1990; Norman et al., 1999). Notably, most investigations on the relationship between symptoms and functioning have been cross-sectional in nature, or focused on the predictive ability of baseline measures.

Recent large-scale studies in schizophrenia have demonstrated modest improvements in psychosocial measures after antipsychotic treatment, with no observed differences between first generation and second generation antipsychotics or between different agents (Guo et al., 2012; Jones et al., 2006; Swartz et al., 2007). With antipsychotics we now have relatively effective treatments for positive symptoms, but as yet no effective strategy for negative symptoms and cognitive impairment (Citrome, 2014). The relatively modest improvements in negative symptoms and cognitive impairment after antipsychotic treatment have been ascribed to improvements in positive symptoms or practice effects, respectively (Davidson et al., 2009; Keefe et al., 2007; Tandon et al., 1993). It seem intuitive to assume that symptomatic improvement translates to improvements in psychosocial functioning although relatively few reports have, in fact, closely examined the nature of this relationship (Buchanan et al., 1998; Smith et al., 2011; Swartz et al., 2007).

Clozapine, the prototype for "atypical" antipsychotics and the agent of choice in treatment-resistant schizophrenia (TRS) has been linked to improvements in symptoms, cognition, functioning, quality of life, suicidality and even employment (Ciapparelli et al., 2003; Kane et al., 1988; Kaneda et al., 2010; Leucht et al., 2013; Meltzer et al., 2003; Meltzer and McGurk, 1999). However, we were able to find only a single study and it reported no relationship between improvement in positive and affective symptoms with improvement in functioning while on clozapine (Buchanan et al., 1998). Addressing this gap, the aim of the present study was to examine the relationship between changes in symptoms and functioning after 6 and 12 weeks of clozapine treatment in a naturalistic setting. The secondary objective was to identify predictors of change in functioning over the same time period. We hypothesized that improvement in symptoms alone only explains a small proportion of the variance observed in improvement in functioning with clozapine treatment.

2. Experimental procedures

2.1. Study setting

Participants included in this study were patients from the Clozapine Registry at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada. Since July 2011, patients initiated on clozapine at CAMH were systematically assessed with clinical scales as part of their routine care. Patients initiated on clozapine at CAMH must have documented failure to at least 2 prior antipsychotic trials. Scales were administered by physicians or one of two nurses linked to the Clozapine program, with inter-rater reliability established through repeated training sessions initiated at the same time. However, no formal statistical test for inter-rater reliability was performed. The present study included participants who were (i) initiated on clozapine at CAMH within the study period 2011–2013; (ii) had a clinical diagnosis of schizophrenia or schizoaffective; and (iii) provided baseline and 6-week post-baseline assessments on the 18-item Brief Psychiatric Rating Scale (BPRS) and the Social and Occupational Functioning Scale (SOFAS) (Goldman et al., 1992; Overall and Gorham, 1962). This study was approved by the Research Ethics Board at CAMH.

2.2. Data collection and clinical assessments

Data regarding age, gender and psychiatric diagnosis prior to clozapine initiation (baseline) were collected. Psychopathology and functioning were assessed using the BPRS and SOFAS, respectively, while current impression of illness severity was assessed with the Clinical Global Impression-Severity of illness (CGI-S). Clinical assessments were performed prior to or within 2 days of clozapine initiation (baseline), and at 6 and 12 weeks of clozapine treatment. A subset of participants was further assessed with the Brief Assessment of Cognition in Schizophrenia (BACS) at baseline (Keefe et al., 2004, 2008).

2.3. Statistical analyses

The BPRS was summarized as factor scores in accordance with a recent meta-analysis of BPRS factor structure in schizophrenia, which reported a 5-factor model (Shafer, 2005). These 5 factors were as follows: positive (conceptual disorganization, grandiosity, hallucinatory behavior and unusual thought content), negative (emotional withdrawal, motor retardation, blunted affect and disorientation), affect (depressive mood, somatic concern, anxiety and guilt feelings), activation (tension, mannerisms and posturing, and excitement), and resistance (hostility, suspiciousness and uncooperativeness). Univariate analyses were used to describe sample characteristics at all study visits and normality assumptions were tested before selection of appropriate statistical test. As the